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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/954,771	10/20/1997	PHILIP w INGham	HMSU-P11-006	6520

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ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	39

DATE MAILED: 07/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
08/954,771	Ingham, PW
Examiner	**Art Unit**
Michael Brannock, Ph.D	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

THE REPLY FILED *Jun 6, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____

3. ☒ Applicant's reply has overcome the following rejection(s):
   see Attachment to Advisory Action

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   see attachment to advisory action

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *123-131 and 133-164*

   Claim(s) objected to: _____

   Claim(s) rejected: _____

   Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

Attachment to Advisory Action

1. Claims 123-165 stand provisionally rejected under the judicially created doctrine of double patenting over claims 11-13 of copending Application No. 08/462386. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: *in vitro* methods of promoting the growth, differentiation and/or survival of neuronal cells by contacting the cells with a sonic hedgehog protein.

Applicant's intention (Paper 28) to provide a terminal disclaimer is acknowledged.

Claim Rejections - 35 USC § 112

2. The rejection of claims 132 and 154 under 35 U.S.C. 112, second paragraph, as set forth in item 9 of Paper 36 is withdrawn in view of Applicants' amendments put forth in Paper 38.

3. Claims 123-165 stand rejected under 35 U.S.C. 112, first paragraph, as set forth previously in item 12 of Paper 36 and in item 13 of Paper 26, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neuronal cells by administering a polypeptide (sonic hedgehog) of SEQ ID NO: 8, 11, 12, and 13

or an N-terminal autoproteolytic portion thereof (as described in the specification), does not reasonably provide enablement for administering a polypeptide other than a polypeptide of SEQ ID NO: 8, 11, 12, and 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, and nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons of record.

Applicant argues that it would not take undue experimentation to determine that hedgehog proteins function in the adult nervous system. Applicant's arguments regarding the use of hedgehog polypeptides in the adult nervous system have been substantially addressed previously. Applicant additionally argues that one of skilled in the art would not be dissuaded from trying to find a way to use the hedgehog polypeptides in the adult because of the teachings in the specification that were pointed to by the examiner, e.g. that hedgehog proteins were known in the art to work only in embryonic tissue and that the specification indicated that hedgehog protein were not expressed in adult tissues. Rather, Applicant asserts that the artisan would be concerned only with the expression of the hedgehog receptor *patched* in the adult. This argument has been fully considered but not deemed persuasive. As set forth previously, the specification discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be

responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Additionally, Applicant essentially admits that the specification does provide any information about patched expression in the adult either. Applicant, provides a pre-filing date reference (Takabatake et al., FEBS Letts 410(485-489)1997) that indicates that Shh and patched are expressed in in adult neural ocular tissues and other adult tissues. Takabatake et al., merely speculate that "judging from their roles in embryos, hh molecules might function in certain cell-cell communications between deferent types of tissues in the adult eye" (see col 1 of page 489). Other - post filing date references, referred to by Applicant, provide more information as to potential roles of hh proteins in the adult, however, as set forth previously, it this type of research and investigation that would need to be performed, e.g. to find neural tissues in the adult, that needs to be performed before the skilled artisan can use the hedgehog polypeptides as claimed. The instant specification ,as well as the prior art at the time of filing, provide only speculations and an invitation to perform this type of research.

Applicant's arguments regarding enablement of methods using amino acid sequence variants of hedgehog polypeptides have been substantially addressed previously. Additionally, Applicant argues that techniques in combinatorial chemistry, etc., have trivialized the construction and screening of protein variants. This argument has been fully considered but not deemed persuasive. The references cited by Applicant regarding combinatorial mutagenesis are each directed to prokaryotic proteins expressed in bacteria wherein a rapid assay system for each

has been well developed in the art. There is no indication, either in the specification nor in the prior art, that the techniques now referred to by Applicant are amenable to use with the proteins encompassed by the instant invention, wherein assays involve integral membrane proteins and/or nervous tissue.

Additionally, the rejection is not based on a lack of understanding as to why the invention works, as alleged by Applicant. The rejection is based on the fact that the specification has failed to provide sufficient guidance to use hedgehog proteins for the growth or promotion of survival of any particular adult nervous tissue, nor how to make variants of hedgehog proteins to be used with embryonic tissue without undue experimentation on the part of one highly skilled in the art.

Conclusion

No claims are allowable.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

July 2, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600